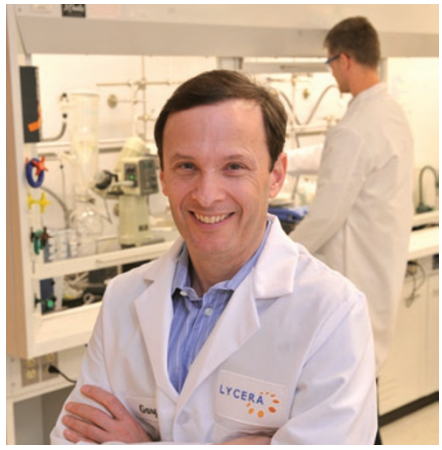
NEWS maker

Lycera

Galvanized by ex-Pfizer researchers, Lycera is pursuing allosteric inhibitors of the mitochondrial ATPase and a nuclear receptor in autoimmune and inflammatory diseases.



Lycera founder Gary Glick.

In June, Lycera announced plans to move into leased space within the former Pfizer Global R&D facility in Ann Arbor, Michigan. It's familiar ground, because many of Lycera's staff once worked at the vast site where Lipitor (atorvastatin), the world's best-selling drug, was developed. In 2006, University of Michigan scientists Gary Glick and Anthony Opipari, who first met by chance in an Ann Arbor supermarket, founded Lycera. After Pfizer closed its vast facility two years later, several of the company's senior scientists joined Lycera; indeed, all but 6 of Lycera's 19 staff once worked for the pharma giant. Their drug development experience will be needed, because Lycera is developing small molecules to challenge Pfizer and other pharmas in autoimmune disease.

Lycera's programs involve one novel target and another pursued by multiple competitors. It epitomizes the sleek and lean business model currently preferred by investors and was able to raise $36 million in a series A financing in 2009. Further funding has come from a collaboration agreement signed in April with Merck that provides the startup with $12 million cash up front, along with undisclosed research support. Glick says the company is looking for new projects for a broad portfolio in immunity, autoimmunity and inflammation.

The company's choice of enzyme target is somewhat surprising. A decade ago, Glick, an organic chemist trained in biochemistry, screened a benzodiazepine library for compounds that killed cultured B cells, and found one, Bz-423, that also reduced disease symptoms in a mouse model of lupus. The compound inhibits the mitochondrial F0-F1-ATPase, the enzyme responsible for the last step in ATP production in mitochondria. Glick's small molecule slows down the respiratory chain, creating conditions favoring the transfer of electrons to oxygen to make superoxide, which triggers apoptosis in chronically activated lymphocytes.

After their first chance encounter in the grocery aisle, Opipari, a gynecologic oncologist and apoptosis researcher, worked in Glick's laboratory for a year before starting his own. They tested the benzodiazepine compound and others in animal models of rheumatoid arthritis, inflammatory bowel disease, lupus and multiple sclerosis. According to Jeff Leiden, managing partner at Clarus Ventures, a venture capital firm in Boston, that participated in Lycera's series A, the company's compounds work in all of them. Glick says toxicity has been minimal and orally bioavailable ATPase inhibitors have now been made, with the expectation of human trials next year.

An obvious worry is that any drug that targets the mitochondrial ATPase, which is expressed in all tissues, will have toxicity, especially in mitochondria-rich organs like the heart, says Toren Finkel, a researcher at the National Institutes of Health. Selectivity for autoreactive lymphocytes is crucial, he says, if those compounds are to be useful autoimmunity drugs.

Glick makes a plausible case for selectivity. First, the compounds are allosteric partial inhibitors, so ATP is still produced, although at a slower rate. Second, Glick has shown in some models that chronically activated T cells typical of autoimmune disease generate ATP mostly through respiration, as opposed to acutely activated lymphocytes that rely more on glycolysis, an anerobic process. This difference may translate into a therapeutic window, because Lycera's compounds generate more superoxide than usual in these respiration-dependent lymphocytes, which also have reduced antioxidant defenses, thus selectively killing them. Leiden says he was convinced the compounds were safe in animals after Glick treated them with high doses for long periods of time without signs of mitochondrial toxicity.

Lycera's second project originated in 2008, when Dan Littman, an immunologist at New York University, approached Leiden with a plan to develop small-molecule inhibitors of the retinoic acid–related orphan nuclear receptor gamma t (RORγt). Littman had earlier shown that RORγ, a transcription factor, is a master regulator of interleukin (IL)-17, producing T helper 17 (Th17) cell differentiation, which are key mediators of autoimmune and inflammatory diseases. Leiden brought Littman and the RORγt project to Lycera, drumming up interest in the 2009 series A financing.

The company has since launched its own screening program for RORγt inhibitors and returned the original intellectual property to New York University. Littman and Lycera severed ties, but Glick still considers him a company cofounder.

By blocking Th17 differentiation, RORγt inhibitors have clear therapeutic potential, and knocking out RORγt in mice does not appear harmful. Glick points out that hitting the transcription factor will effectively block all cytokines released by Th17 cells, and thus might be more effective than monoclonal antibodies targeting only the cytokine IL-17 and its receptor.

A nagging concern, however, is that little is known about RORγ function outside the immune system. What's more, several other companies are also developing small-molecule RORγt inhibitors. According to Leiden, Lycera is ahead in the race. The company identified more specific inhibitors, he says, because of a rigorous screening funnel, and moved molecules quickly from chemistry to biology and back to refine those compounds.

Lycera's ATPase and RORγt inhibitors will need to compete against very effective small-molecule Janus-associated kinase (JAK) inhibitors in late-stage development at Pfizer and other companies (*Nat. Biotechnol.* **29**, 467–468, 2011). Glick says his compounds are less likely than JAK inhibitors to be immunosuppressive and should be safer.

At Lycera, every researcher except Glick still works at the bench. Collectively, they're responsible for 14 Pfizer compounds currently in clinical development. The question is whether, working again in Pfizer's old laboratories, they can duplicate their success and outcompete the pharma giant.

Ken Garber *Ann Arbor, Michigan.*